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ORIGINAL PAPER

Acute kidney injury caused by consumption of melamine-contaminated infant formula in 47 children: a multi-institutional experience in diagnosis, treatment and follow-up

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Abstract Since the spring of 2008, an epidemic of urinary tract stones was noted among children in China. This is believed to be associated with consumption melamine-contaminated powdered formula. A few patients presented with acute kidney injury (AKI) due to bilateral renal or ureteral calculi requiring surgical intervention to relieve the obstruction. We retrospectively analyzed clinical and laboratory data, ultrasonograms and treatment methods in children with melamine-induced urolithiasis and AKI who were hospitalized at seven hospitals from September to November 2008 in Gansu Province, China. Treatment given included conservative treatment, cystoscopic or urethroscopic lithotripsy, retrograde ureteral catheterization, ureterolithotomy and nephrostomy. Patients were monitored postoperatively with data of ultrasonography, urinalysis and blood and urine biochemistry. The mean age of the 47 children was 10 months (mean ± SD, 10.83 ± 5.11 months). Thirty-four (72.34%) were male. Calculi size ranged from 3 to 14 mm in diameter. Nine patients (19.15%) were successfully treated with conservative treatment; 32 (68.09%) underwent retrograde ureteral catheterization and eight had simultaneous cystoscopic or urethroscopic stone removal; four were successfully treated with ureterolithotomy, and 1 underwent percutaneous nephrostomy. Thirty-eight patients were followed up for a mean ± SD of 18.50 ± 5.27 months and their renal functions were found to have completely recovered. Five (13.16%) cases had residual renal stones with diameter ranging from 2 to 4 mm. Therefore, this study has demonstrated that melamine-induced urolithiasis could lead to AKI. Removing obstruction promptly by surgical intervention has been found to be effective with satisfactory outcomes observed at mean follow-up period of 18-month. However, residual renal stone remained in 13.16% of the cases which required continued close observation.

Keywords Urolithiasis · Melamine infants · Acute kidney injury

Abbreviations

AKI	Acute kidney injury
BUN	Blood urea nitrogen
Cr	Creatinine

Introduction

Starting from April 2008, an increasing number of young children had been diagnosed with urinary tract stones after consuming melamine-contaminated infant formula in China [1]. They presented with signs of restlessness, upper respiratory infections, vomiting, diarrhea, gross or microscopic hematuria or history of stone passage during urination. A number of cases were diagnosed to have acute kidney injury (AKI) (previously called acute renal failure) and further accompanying conditions included oliguria, anuria and edema. Conservative treatment consists of increase in fluid intake, administration of sodium bicarbonate (urine alkalization) to aid stone passage, and continuous renal replacement therapy. Surgical options including retrograde ureteral catheterization, cystoscopic or urethroscopic lithotripsy, and ureterolithotomy were often performed to relieve the obstruction [2–4]. Although the short-term outcome had been reported to be satisfactory [2], the long-term

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prognosis remained unclear. In this study, we explored the clinical features and long-term efficacy of treatment in young children with AKI caused by melamine-contaminated infant formula.

Patients and methods

Patients

From April 2008 to November 2008, a total of 47 children with melamine-induced urolithiasis and AKI were diagnosed and treated in seven institutions in Gansu Province, China, including Lanzhou University Second Hospital, First Hospital of Chinese People's Liberation Army, People's Hospital of Gansu Province, Tenth Hospital of Chinese People's Liberation Army, Wuwei City Liangzhou District People's Hospital, Jiuquan City People's Hospital and The General Hospital of Coal Industry Limited Corporation of Jingyuan. All subjects had ultrasonographic evidence of urinary tract calculi and history of consuming melamine-contaminated infant formula. Calculi size, location and any associated hydronephrosis were recorded. Data from urinalysis and routine serum chemistry, including blood urea nitrogen (BUN), serum creatinine (Cr), and uric acid were collected from each patient. AKI was diagnosed when Cr concentration had absolute increased greater than 26.4 μmol/L (0.3 mg/dL), or a percentage increased of ≥50% within 48 h, or urine output decreased to <0.5 mL/(kg h) within 6 h [5]. This study was approved by the Ethics Committee of Second Hospital of Lanzhou University. Written consents for the study were obtained from all parents or guardians.

Methods and treatments

All patients were treated according to the guidelines as recommended by the Chinese Ministry of Health and included immediately stop of consumption of melamine-contaminated formula [6]. Melamine-induced urinary stones were soft and easy to remove. So conservative treatment was the first line therapy, which included intravenous fluid infusion and use of diuretics to increase urine output (30 mL/kg of 0.9% saline solution and 1 mg/kg furosemide), urine alkalization (to pH > 6.5) with 5% sodium bicarbonate (5 mL/kg daily diluted in 1.4 of 5% glucose solution), and urethral catheterization if necessary. Antibiotics were administered to patients with fever, diarrhea or urinary tract infection. Blood biochemistry and urinalysis were monitored weekly, with ultrasonography performed within 3–5 days. For patients presenting with BUN of >15 mmol/L, or Cr of >355 μmol/L, or serum potassium of >5.5 mmol/L, surgical intervention to relieve the obstruction was performed immediately. Each patient was evaluated for apparent obstruction and its location. To those with obstructing bladder or urethral calculi, cystoscopic or urethroscopic lithotripsy was preformed. Retrograde catheterization into the ureter via cystoscope was performed if AKI was caused by bilateral ureteral and/or renal calculi obstruction. Ureterolithotomy or percutaneous nephrostomy was performed in hospitals lacking minimally invasive endoscopic expertise.

Follow-up

We followed up the children suffering from melamine-induced urolithiasis and AKI from March to May 2010. Ultrasound examination of urinary tract was performed using an ultrasonography system (ProSound SSD-5000SV, Aloka) with an attached scanner monitor (5–6 MHz). Patients with anxiety were treated with oral 10% chloral hydrate (0.5 mL/kg). BUN, Cr and uric acid levels in blood samples were analysed using a 7600-010 Automatic Analyzer (Hitachi, High-Tech Science Systems Corporation, Japan). Urinalysis was performed using Multistix 10SG strips (Siemens, Tarrytown, NY, USA) and read by Clinitek 500 Analyzer (Bayer, Elkhart, IN, USA). Microscopic examination was performed using an inverted microscope. Urine microalbumin, β-2-microglobulin and α-1-microglobulin levels in urine samples were measured using a radioimmunoassay kit (Jiuding, Tianjin, China). All the samples were tested within 3 h of collection. Reference intervals are as follows: BUN 1.8–6.5 mmol/L; Cr 20–60 μmol/L; uric acid 119–327 μmol/L; microalbumin 0–19 μg/mL; α-1-microglobulin 0–12 μg/mL; β-2-microglobulin 0–154 ng/mL [6, 7].

Statistical analysis

SPSS 17.0 software was used to analyze the data. Numerical variables that were normally distributed were expressed as mean ± SD and analyzed by Student's t test. Categorical variables were noted as number and percentages and analyzed by Chi-square test. Results were considered to be statistically significant if $P < 0.05$.

Results

Clinical features

Forty-seven children with melamine-induced urolithiasis and AKI were included in this study (34 males, 13 females). The mean age was 10.83 ± 5.11 months. Duration of consumption of melamine-contaminated infant formula ranged from 3 to 23 months (9.30 ± 3.89 months, mean ± SD). All patients presented with complaints of

Table 1 Success rates of treatment

Calculi type	Conservative management	Cystoscopic or urethroscopic lithotripsy	Retrograde ureteral catheterization	Ureterolithotomy	Nephrostomy	Total
Bilateral renal	5/13 (38.5)	–	17/20 (85.0)	–	1/1 (100)	25/29 (86.2)
Unilateral renal	2/7 (28.6)	–	9/10 (90.0)	–	–	12/15 (80.0)
Bilateral ureteral	3/10 (30.0)	–	19/20 (95.0)	4/4 (100)	1/1 (100)	30/32 (93.8)
Unilateral ureteral	2/5 (40.0)	–	4/4 (100.0)	–	–	6/6 (100)
Bladder	3/7 (42.9)	5/5 (100)	–	–	–	11/11 (100)
Urethral	2/7 (28.6)	5/5 (100)	–	–	–	8/8 (100)
Total	9/21 (42.9)	8/8 (100)	28/32 (87.5)	4/4 (100)	1/1 (100)	40/47 (85.1)

Data are expressed as no./total no. (%)

dysuria, oliguria or anuria; 23 experienced diarrhea; 18 had fever and 12 presented with gross hematuria. Fourteen patients had a medical history of turbid urine with sediments or stones. AKI was diagnosed in each case and urinary stones were confirmed by ultrasonography. The mean duration of anuria was 54.75 ± 30.71 h (range 8–120 h). Calculi ranged in diameter from 3 to 14 mm (7.22 ± 2.09 mm, mean ± SD). None of the patients had accompanying anatomical malformations of the urinary system.

Further investigations revealed presence of stones in bilateral kidneys (29 cases), unilateral kidney (15 cases), bilateral ureters (32 cases), unilateral ureter (6 cases), bladder (11 cases) and the urethra (8 cases). The male to female ratios were 2.6:1.0 among kidney calculi and 2.5:1.0 among ureteral calculi, respectively. However, all bladder and urethral calculi occurred only in boys. There were no significant difference between the genders of the children with respect to stone size and age. Forty-three cases (91.5%) had co-existing renal, ureteral, bladder and/or urethral calculi, which is obviously more than common oxalate calcium calculi. Twenty-nine had bilateral hydronephrosis and three had unilateral hydronephrosis. A total of 39 patients presented with AKI at admission; 8 developed AKI while receiving conservative treatment (increased fluid intake and administration of sodium bicarbonate). The mean levels of BUN, serum Cr and uric acid were 25.17 ± 10.28 mmol/L, 433.73 ± 160.17 and 632.81 ± 258.51 μmol/L, respectively. Only ten calculi samples were collected from these patients and melamine was detected in all by high-performance liquid chromatography (HPLC) (Agilent 1100, Germany).

Treatment and outcome

Of the 47 patients, 9 (19.15%) were successfully treated with conservative treatment and 31 (65.96%) were successfully treated with retrograde ureteral catheterization (of these, 8 simultaneously received cystoscopic or urethroscopic removal). Because of lack of available minimally invasive treatment, four patients were treated with ureterolithotomy, and remaining one patient was treated by percutaneous nephrostomy (bilateral renal and ureteral calculi). After different treatments, the obstructive symptoms were relieved and the blood biochemistry parameters returned to normal in most cases. However, one infant died following rapidly progressing obstructive renal failure during conservative treatment; another succumbed due to severe infection 3 days after retrograde ureteral catheterization. There were no major surgical complications. Further details of treatment and follow-up are given below. Success rates of the different treatment options are shown in Table 1.

Conservative management

Twenty-one children were treated with conservative therapy (sodium bicarbonate and increased fluid intake) to facilitate stone passage. Nine patients (42.9%) had successful stone passage and the urine output significantly increased within 24 h of treatment. Among them, four infants with bladder and/or urethral stones (2 with bladder calculi, 1 with urethral calculi; 1 with co-existing bladder and urethral calculi) required urethral catheterization to remove the calculi. One infant died following rapidly worsening obstructive renal failure during treatment; the remaining 11 patients required surgical intervention to relieve the obstruction because of lack of improvement following conservative management.

Cystoscopic or urethroscopic lithotripsy

After general anesthesia with ketamine, a pedo-cystoscope was inserted via the urethra to the bladder. Sand-gravel-like calculi were found and were successfully cleared by continuous irrigation with saline in eight patients (3 with bladder calculi, 3 with urethral calculi, and 2 with coexisting bladder and urethral calculi). All patients also had accompanying

Table 2 Laboratory data

Result	Before treatment	At follow-up	*P* value
BUN (mmol/L)—mean ± SD	26.05 ± 9.77	4.74 ± 1.10	<0.001
Cr (μmol/L)—mean ± SD	442.29 ± 154.13	32.26 ± 11.25	<0.001
Uric acid (μmol/L)—mean ± SD	634.52 ± 276.54	210.05 ± 46.32	<0.001
Proteinuria—no. of cases (%)	1 (2.6)	0	1.00
Occult blood—no. of cases (%)	14 (36.8)	5 (13.2)	0.03
Microscopic hematuria—no. of cases (%)[†]	10 (26.3)	2 (5.3)	0.03
Leukocyturia—no. of cases (%)[†]	11 (28.9)	0	<0.001
α-1-microglobulin (μg/mL)	0.35 ± 0.15	0.36 ± 0.15	0.44
Increased microalbumin (>19 μg/mL)—no. of cases (%)	3 (7.9)	2 (5.3)	1.00
Increased β_2-microglobulin (>154 ng/mL)—no. of cases (%)	6 (15.8)	5 (13.2)	1.00

[†] Microscopic hematuria = >3 red blood cells per high-power field; leukocyturia = >5 white blood cells per high-power field

renal or ureteral calculi, so retrograde ureteral catheterization was simultaneously performed (2 with renal calculi, 1 with urethral calculi, 5 with co-existing renal and ureteral calculi). Urine volume significantly improved in these patients within 24 h of treatment.

Retrograde ureteral catheterization

A 4Fr ureteral catheter was retrogradely inserted into each ureter via cystoscope to guide urine and calculi flow. The catheter was then removed and a guide wire was inserted for the placement of a 4Fr double pigtail ureteral stent. The double pigtail ureteral stents were removed by pedo-cystoscopy after 4 weeks.

A total of 32 patients underwent retrograde catheterization. Of these, eight patients underwent simultaneous retrograde ureteral catheterization after cystoscopic or urethroscopic lithotripsy as described above. The obstructive symptoms were relieved immediately and urine drainage was successful in all patients. However, one patient died from severe infection 3 days after retrograde ureteral catheterization.

Ureterolithotomy and nephrostomy

Under general anesthesia, incisions were made on both ureters to remove the stones and guide the insertion of 4Fr single pigtail ureteral stents into the ureters. The stents were removed after 4 weeks. Four patients successfully underwent bilateral ureterolithotomy with full recovery after the operations. Ultrasound-guided bilateral nephrostomy was performed in one patient with bilateral renal and ureteral calculi. Urine drained through nephrostomy tubes accompanied by expelling of sand-gravel-like calculi. After intermittent irrigation of the renal pelvis with saline, the residual renal and ureteral stones were eventually expelled and the nephrostomy tubes were withdrawn 1-week later.

Follow-up outcome

Mean follow-up duration in 38 patients was 18.50 ± 5.27 months. Two patients died during hospitalization, one died 14 months later of heart failure complicated by severe pneumonia. The remaining six patients were lost for follow-up because of changes of contact information and addresses.

Of the 38 patients, 5 (13.16%) had residual renal calculi at follow-up (4 males, 1 female). The stone diameter ranged from 2 to 4 mm (mean ± SD, 0.31 ± 0.06). Two patients of there were treated conservatively and three had retrograde ureteral catheterization. Because of the small stone size and lack of obstructive symptoms, they were instructed to take adequate water daily with scheduled follow-up ultrasound examinations every 3 months.

Blood biochemistry data in all the subjects were within normal ranges at follow-up (Table 2). However, no significant difference was observed in the urinalysis data. Concentrations of α-1-microglobulin, a marker for re-absorptive function of proximal convoluted tubule, were all within normal ranges (reference interval: 0–12 μg/mL) prior to and after treatment. Slightly elevated levels of urine microalbumin were observed in two subjects (19.97 and 20.35 μg/mL; reference interval: 0–19 μg/mL), indicating damage to the renal glomerulus. Raised levels of urine β-2-microglobulin, representing renal tubular lesions, were observed in five subjects (from 167.9 to 307.1 ng/mL; reference interval: 0–154 ng/mL).

Discussion

Pediatric urolithiasis is relatively rare and often occurs in individuals with underlying metabolic abnormality. In 2008, an abnormally high prevalence of kidney stones in infants was identified in our hospital. Some children were diagnosed of AKI and accompanying symptoms including oliguria, anuria and edema. On September 12, 2008, the Chinese government authorities announced that some manufacturers had added melamine to powdered milk formula in order to falsely increase protein contents. In less than 2 months, 294,000 cases of melamine-associated kidney stones were reported, with over 51,900 babies and infants hospitalized throughout China. At least six confirmed deaths were linked to consumption of melamine-contaminated milk formula [8]. The relationship between this epidemic of urinary stones and consumption of melamine-contaminated milk powder was later confirmed [6, 7]. Indeed, melamine was detected in ten expelled calculi samples by HPLC in our study.

Melamine (C3H6N6), also known as tripolycyanamide, is widely used industrially in the production of glues and plastics [9, 10]. However, as melamine has a 66% nitrogen content, it can be used to falsely increase protein levels in foodstuffs [6]. In March 2007, there was a large outbreak of renal failure in cats and dogs in America associated with melamine and cyanuric acid-containing pet food [11]. Animal experiments have revealed that 90% of melamine is rapidly eliminated by the kidneys [12]. However, when combined with cyanuric acid, melamine can form extremely insoluble crystals, which probably led to the formation of urinary stones causing renal failure and death in some animals [13, 14]. Melamine is slightly soluble in water and it can form macromolecular compounds by adhering to and aggregating with other substances [15], the likely mechanism for its ability to form calculus. Indeed, analysis of urinary calculi found in humans after consumption of melamine-contaminated milk powder showed that the main components in the stones were melamine and uric acid [2, 7]. Melamine–uric acid calculi are relatively radiolucent and cannot be easily detected by routine X-ray. Ultrasonographic characteristics of these calculi were less echogenic, sand-like and less dense. Although non-contrast CT is clearly the most sensitive imaging modality for detecting stone. However, ultrasonographic usually is widely available, faster, inexpensive, and poses no risk of radiation exposure. Therefore, the diagnostic approach and follow-up of patients mainly depend on the use of ultrasonography [3, 16].

Most children with melamine-associated urolithiasis are asymptomatic or mildly symptomatic and diagnosis is made based on guidelines from the World Health Organization and the Ministry of Health in China [1, 17, 18]. Diagnostic criteria include: (1) consumption of melamine-contaminated infant milk formula; (2) presence of one or more clinical manifestations such as unexplained crying (especially during urination), vomiting, gross or microscopic hematuria and turbid urine with sediments or stones; (3) normal results of parathyroid hormone test; (4) ultrasonographic evidence of urolithiasis. Further diagnosis and evaluation of AKI is based on extensive laboratory analysis data including serum Cr, BUN, uric acid, serum electrolytes and urinalysis, as well as actual clinical presentations such as oliguria, anuria, edema, nausea, vomiting and loss of appetite.

AKI, previously referred to as acute renal failure, has traditionally been recognized as a reversible increase in the concentration of serum Cr and nitrogenous waste products due to the failure of the kidneys to regulate fluid, electrolyte and acid-base balance [19]. The etiology of AKI is classified into three groups: pre-renal, intrinsic and post-renal [20]. Post-renal AKI can result from obstruction of melamine-induced urolithiasis, generally involving the kidney and/or ureters bilaterally, and occasionally in urethra.

Our study demonstrated a 2.6:1.0 male to female ratio of children with melamine-induced urolithiasis and AKI. The finding is consistent with a survey on population distribution of melamine-induced kidney stones complicated by acute obstructive renal failure in China [4]. All bladder and urethral calculi occurred in boys. However, there were no significant differences between the gender of the children with respect to stone size, response to the given therapy and stone residual rates (not stone recurrence rates) during follow-up. The fact that 43 cases (91.5% of cases) had co-existence of renal, ureteral, bladder and/or urethral calculi indicates that multiple organ involvement of melamine-induced calculi is obviously more than common oxalate calcium calculi. Since melamine-induced urolithiasis were soft and friable, initial conservative management focuses on intravenous fluid infusion and diuresis to increase urine output, urinary alkalinization, and urethral catheterization for urethral obstruction. But when BUN is greater than 15 mmol/L, or Cr is greater than 355 μmol/L, or serum potassium is greater than 5.5 mmol/L, surgical intervention to relieve the obstruction is extremely important for prompt recovery and to avoid permanent damage to renal function. Prompt surgical interventions proved to be effective in treating associated symptoms and improving renal function. In children with AKI and >48 h of oliguria or >24 h of anuria, dialysis was recommend to help normalize clinical blood biochemistry [4, 21]. However, none of the subjects in our study underwent dialysis because of lack of resources in local hospitals.

A total of 38 (81%) patients were successfully followed up (mean 18 months). All had normal BUN and Cr during follow-up. Five patients (13.16%) had residual renal calculi

with diameter ranged from 2 to 4 mm and they were monitored closely by quarterly ultrasonography. However, none of children had stone recurrence or regrowth. We acknowledge that the disadvantage of this study is its retrospective, multi-institutional nature, but we do not want to see more such unfortunate events occur.

In conclusion, melamine-induced urolithiasis could easily lead to AKI, which is rarely seen in general urolithiasis. Our study shows that most patients do well with prompt treatment. Obstruction caused by melamine-induced calculi should be treated promptly with surgical intervention in order to restore renal function, especially in situations where dialysis is unavailable. Asymptomatic residual renal calculi persisted in 13.16% of patients who may need close observation.

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